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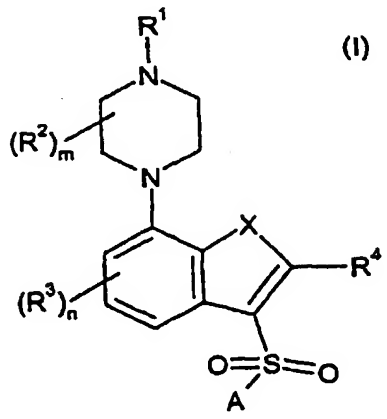
(54) Title: 3-ARYLSULFONYL-7-PIPERAZINYL- INDOLES, -BENZOFURANS AND -BENZOTHIOPHENES WITH 5-HT6 RECEPTOR AFFINITY FOR TREATING CNS DISORDERS



(I)

(57) Abstract: The invention relates to novel compounds of formula (I) having affinity for the 5-HT_6 receptor preparation, to compositions containing them and their use in the treatment of various disorders, including CNS disoders.

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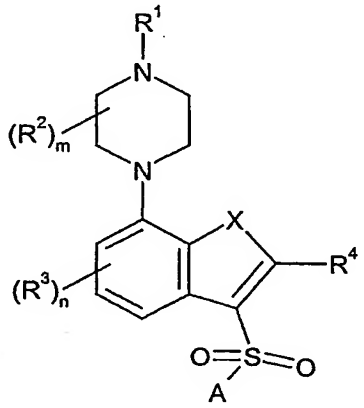
3-ARYLSULFONYL-7-PIPERAZINYL- INDOLES, -BENZOFURANS AND -BENZOTHIOPHENES WITH 5-HT6 RECEPTOR AFFINITY FOR TREATING CNS DISORDERS

This invention relates to novel indole compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081 discloses a series of aryl sulphonamide compounds that are said to be 5-HT_6 receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. GB-2341549, WO 99/47516 and WO 99/65906 all disclose a series of indole derivatives that are claimed to 5-HT_6 receptor affinity.

A structurally novel class of compounds has now been found which also possess 5-HT_6 receptor affinity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;
R^3 independently represents hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;
R^4 represents hydrogen or C_{1-6} alkyl;
R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
m represents an integer from 1 to 4, such that wherein m is an integer greater than 1, said R^2 groups may optionally be linked to form a group CH_2, $(CH_2)_2$ or $(CH_2)_3$;
n represents an integer from 1 to 3;
X represents NH, N-C_{1-6} alkyl, O or S;
A represents a group $-Ar^1$ or $-Ar^2Ar^3$;

Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

When Ar^1, Ar^2 or Ar^3 are substituted they are preferably substituted by 1 or 2 substituents.
Preferably, R^1 represents hydrogen or methyl. Most preferably, R^1 represents hydrogen.
Preferably, R^2 represents hydrogen.
Preferably, R^3 represents hydrogen or halogen (such as chlorine, eg. 4-, 5- or 6-chlorine). Most preferably, R^3 represents hydrogen.
Preferably, R^4 represents hydrogen or methyl. Most preferably, R^4 represents hydrogen.

Preferably, X represents NH, N-CH_3, O or S. Most preferably, X represents N-CH_3.
Preferably, m represents 1.
Preferably n represents 1 or 2. Most preferably, n represents 1.
Preferably, A represents Ar^1.
When Ar^1 represents a heteroaryl group it is preferably N-linked indole, such as 1H-indol-1-yl, or C-linked pyridyl such as 2-pyridyl, each of which may be optionally substituted.
When Ar^1 represents an aryl group it is preferably optionally substituted phenyl.
Preferably, Ar^1 is optionally substituted with one or more halogen (particularly 2- or 3-chloro and 2-, 3- and 4-fluoro), cyano (particularly 2-cyano), trifluoromethyl (particularly 2-trifluoromethyl), methyl, trifluoromethoxy or acetyl groups. More preferably, Ar^1 is phenyl optionally substituted with one or more halogen (particularly 2 or 3-chloro and 2, 3 and 4-fluoro), cyano (particularly 2-cyano) or trifluoromethyl (particularly 2-trifluoromethyl) groups.
Most preferably, Ar^1 represents phenyl substituted by one halogen, such as chlorine (especially 3-chlorine).
Preferred compounds according to the invention include examples E1-E26 as shown below, or a pharmaceutically acceptable salt thereof.

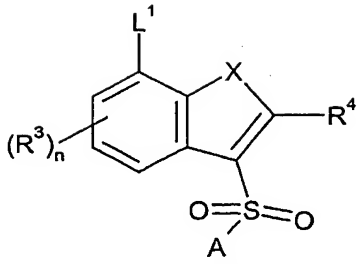
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

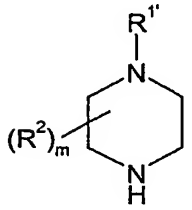
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

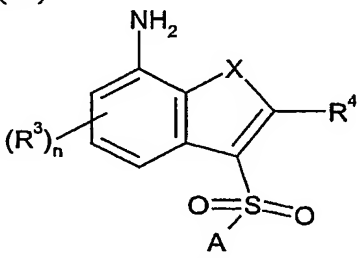
with a compound of formula (III)



(III)

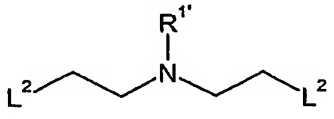
wherein $R^{1'}$ is as defined above for R^1 or an N-protecting group, R^2, R^3, R^4, A, X, m and n are as defined above and L^1 represents a suitable leaving group, such as a halogen atom (eg. bromine) or a trifluoromethylsulfonyloxy group; or

(b) forming a compound of formula (I) wherein R^2 represents hydrogen which comprises reacting a compound of formula (IV)



(IV)

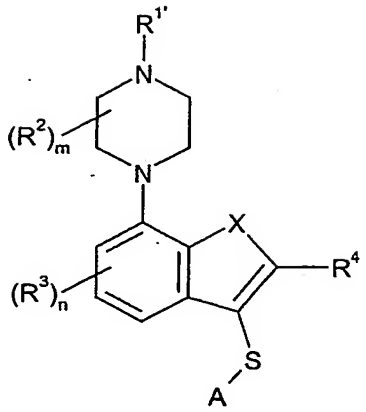
with a compound of formula (V)



(V)

wherein $R^{1'}$ is as defined above for R^1 or an N-protecting group, R^3, R^4, X, A and n are as defined above and L^2 represents a suitable leaving group, such as a halogen atom; or

(c) oxidation of a compound of formula (VI)



(VI)

wherein $R^{1'}$ is as defined above for R^1 or an N-protecting group and R^2, R^3, R^4, A, m, n and X are as defined above; or

(d) deprotecting a compound of formula (I) which is protected;
and optionally thereafter interconversion to other compounds of formula (I).

The N-protecting group used may be any conventional group eg. t-butyloxycarbonyl (Boc) or benzyloxycarbonyl.

Process (a) typically comprises the use of a suitable base, such as sodium *t*-butoxide or cesium carbonate in the presence of a palladium catalyst (eg. palladium (II) acetate or tris(dibenzylideneacetone)dipalladium (0) in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in a suitable solvent such as dioxan or dimethylformamide.

Process (b) typically comprises the use of a suitable base, such as sodium carbonate and the use of a suitable solvent such as *n*-butanol.

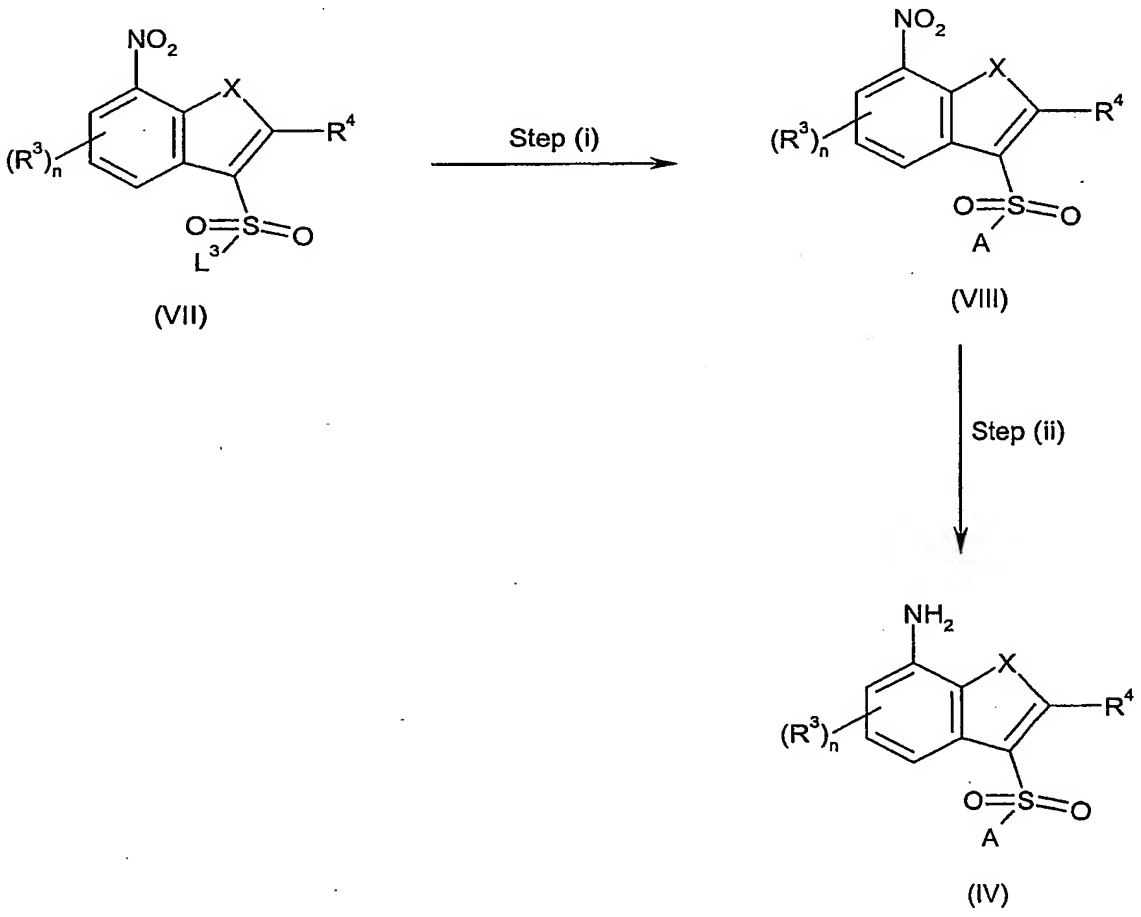
Process (c) typically comprises the use of an oxidising agent, eg. hydrogen peroxide or a peracid reagent, such as peracetic or 3-chloroperbenzoic acid.

In process (d), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid. A further amine protecting group includes methyl which may be removed using standard methods for N-

dealkylation (eg. 1-chloroethyl chloroformate under basic conditions followed by treatment with methanol).

Interconversion of compounds of formula (I) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, *N*-dealkylation of a compound of formula (I) wherein R^1 represents an alkyl group to give a compound of formula (I) wherein R^1 represents hydrogen. A further example of interconversion may include the alkylation of a compound of formula (I) wherein X represents NH to a compound of formula (I) wherein X represents N-C_{1-6} alkyl. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion.

Compounds of formula (IV) may be prepared according to the following process:



(VII) (VIII) (IV)

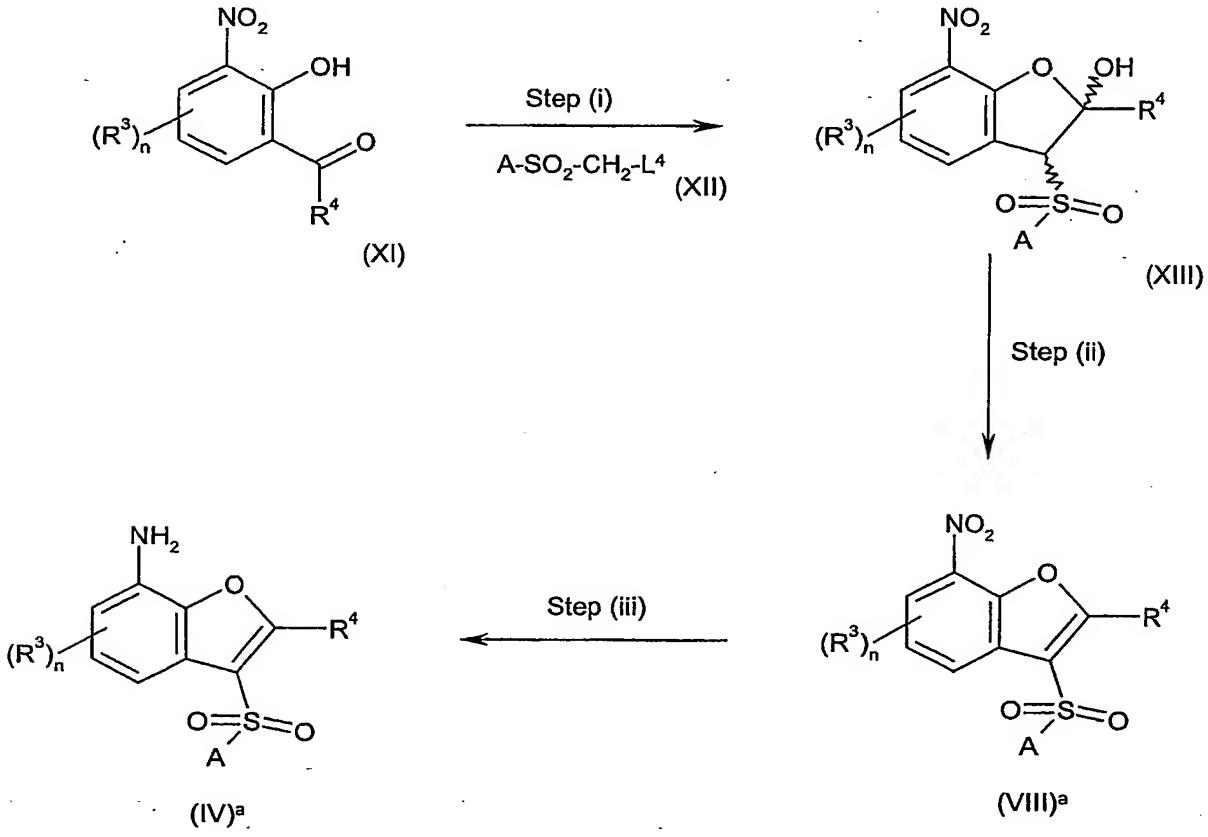
wherein R^3, R^4, X, A and n are as defined above and L^3 represents a suitable leaving group, such as a halogen atom (eg. a fluorine or chlorine atom).

Step (i) typically comprises the reaction of a compound of formula (VII) with a compound of formula A-M, wherein A is as defined above and M represents a metal containing moiety, such as sodium, lithium, magnesium halide or zinc halide.

Step (ii) typically comprises reduction of a compound of formula (VIII), for example using hydrogenation in the presence of a suitable catalyst such as palladium on carbon.

It will be appreciated that compounds of formula (II) may be prepared in an analogous process to that of step (i) above.

Compounds of formula (IV) where X represents O may be more advantageously prepared according to the following process:



wherein R^3, R^4, A and n are as defined above and L^4 represents a suitable leaving group, such as a halogen (eg. chlorine).

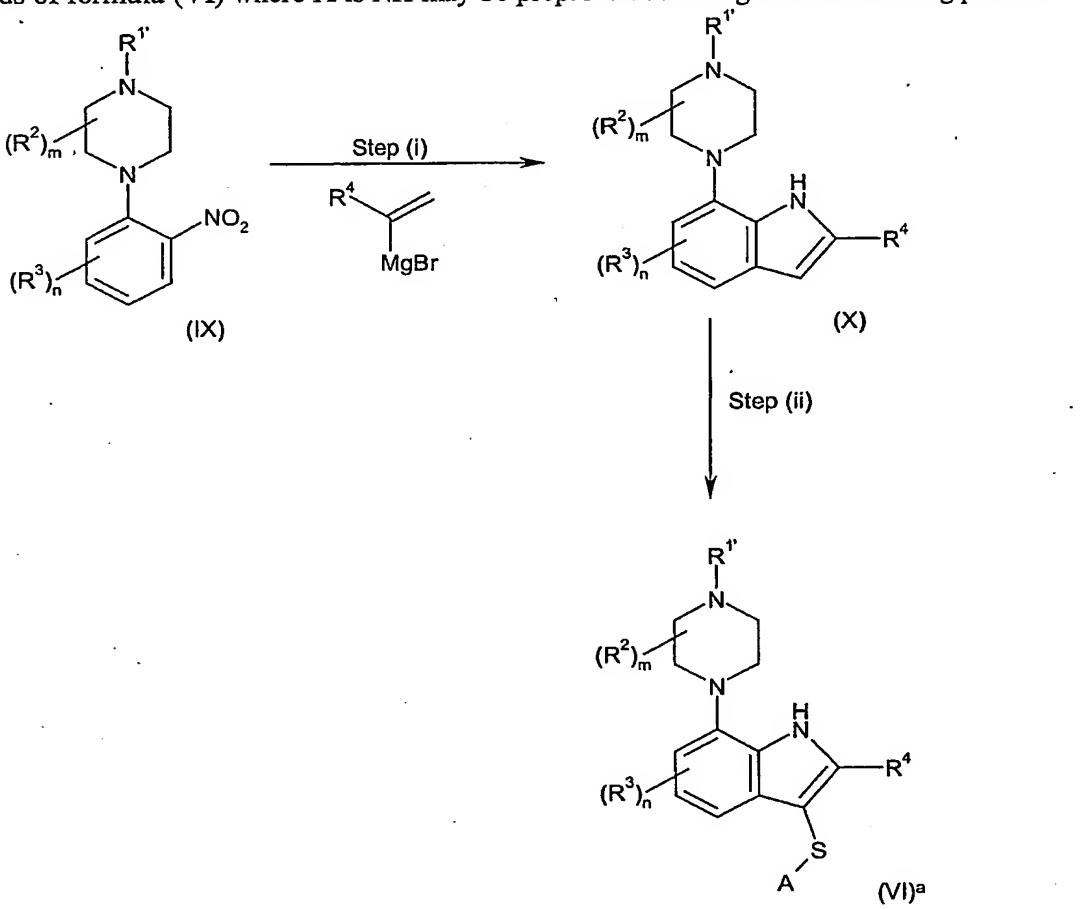
Step (i) comprises reaction of a compound of formula (XI) with a compound of formula (XII) in the presence of a base such as potassium t-butoxide in a suitable solvent such as N,N-dimethylformamide at an appropriate temperature, e.g. –40 °C.

Step (ii) comprises use of a strong acid such as sulfuric acid in a suitable solvent such as acetic acid at an appropriate temperature, e.g. 60 °C.

Step (iii) typically comprises reduction of a compound of formula (VIII)[a], for example using hydrogenation in the presence of a suitable catalyst such as palladium on carbon.

Other compounds of formula (VIII) are known or may be prepared by methods analogous to those described in the literature or analogous to those described above.

Compounds of formula (VI) where X is NH may be prepared according to the following process:

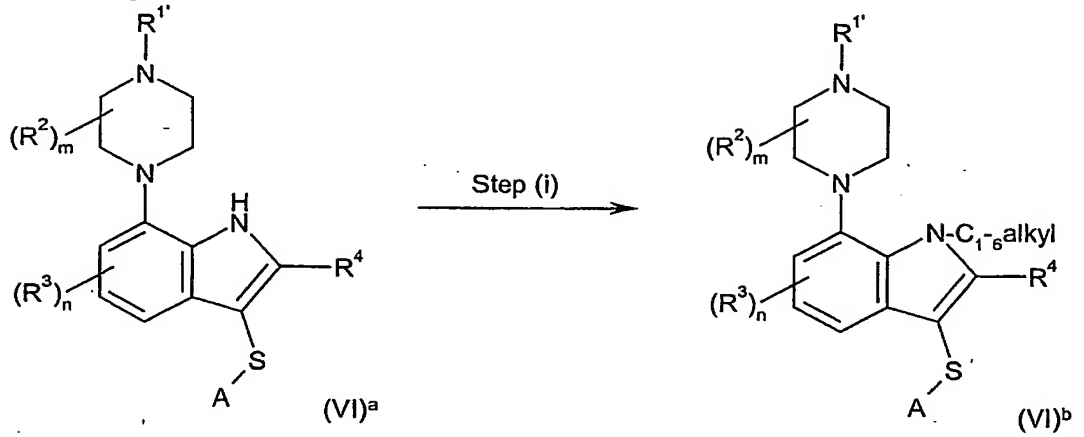


wherein $R^{1'}$ is as defined above for R^1 or an N-protecting group, eg. benzyloxycarbonyl (Boc), and R^2, R^3, R^4, A, m and n are as defined above.

Step (i) typically comprises the use of a solvent eg. tetrahydrofuran at a suitable temperature, eg. -40°C.

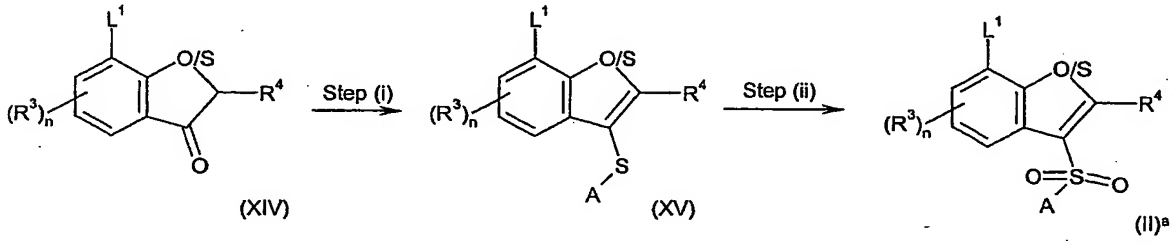
Step (ii) typically comprises the use of a base, eg. sodium hydride followed by reaction of a compound of formula A-S-S-A, wherein A is as defined above in a solvent such as *N,N*-dimethylformamide at a suitable temperature, eg. 20°C.

Compounds of formula (VI) wherein X represents N-C_{1-6} alkyl may be prepared according to the following process:



Step (i) typically comprises the use of a base, eg. sodium hydride, potassium hydroxide or sodium hydroxide followed by reaction with an appropriate C_{1-6}alkylating agent such as methyl iodide or dimethyl sulphate in a solvent such as *N,N*-dimethylformamide or acetone at a suitable temperature e.g. 20 °C.

Compounds of formula (II) wherein X represents O or S may be prepared according to the following process:



wherein R^3, R^4, A, n and L^1 are as defined above.

Step (i) typically comprises reaction with a compound A-SH, where A is as defined above, in a suitable solvent such as benzene in the presence of an acid such as p-toluenesulfonic acid at an appropriate temperature (e.g. at reflux).

Step (ii) typically comprises the use of an oxidising agent such as monoperoxyphthalic acid or 3-chloroperbenzoic acid in a suitable solvent system, e.g. a mixture of methanol and dichloromethane.

Other compounds of formula (II) are known or may be prepared by methods analogous to those described in the literature or analogous to those described above.

Compounds of formula (III), (V), (VII), (IX), (XI), (XII) and (XIV) are either known or may be prepared in accordance with known or analogous procedures. It will be appreciated that compounds of formula (XIV) may also exist as the hydroxy tautomer.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have 5-HT_6 receptor activity and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations,

powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three times a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1: 3-(1*H*-Indole-1-sulfonyl)-7-nitro-1*H*-indole (D1)

To a stirred suspension of sodium hydride (0.46 g, 11.5 mmol, 60% suspension in oil) in dimethylformamide (10 ml) was added dropwise 1*H*-indole (1.34 g, 11.5 mmol) as a solution in dimethylformamide (5 ml). After stirring for 20 minutes, a solution of 7-nitro-1*H*-indole-3-sulfonyl chloride (Mandur *et al.* Chem. Heterocycl. Compd. (Engl. Transl.); **1990**, *26*, 1116-1120, 2.0 g, 7.7 mmol) in dimethylformamide (5 ml) was added dropwise and the resulting mixture was left to stir for 15 hours. The reaction mixture was then diluted with dichloromethane (100 ml) and washed with water (2x50 ml), brine (50 ml), dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with dichloromethane to afford the title compound (D1) (88 mg, 77%), MS: m/z $(M-H)^-$ 339, $C_{16}H_{11}N_3O_4S$ requires 340.

Description 2: 3-(1*H*-Indole-1-sulfonyl)-1*H*-7-indol-7-ylamine (D2)

3-(1*H*-Indole-1-sulfonyl)-7-nitro-1*H*-indole (D1) (1.0 g, 2.9 mmol) was dissolved in ethanol (50 ml) followed by addition of palladium catalyst (0.2 g, 10% Pd/C). The resulting mixture was stirred under an atmosphere of hydrogen for 15 hours followed by filtration (CELITE) and *in vacuo* removal of solvent. This provided the title compound (D2) (0.73 g, 80%), MS: m/z $(M-H)^-$ 309, $C_{16}H_{13}N_3O_2S$ requires 310.

Description 3: 4-(1H-Indol-7-yl)piperazine-1-carboxylic acid tert-butyl ester (D3)

A solution of 4-(2-nitrophenyl)piperazine-1-carboxylic acid tert-butyl ester [(For synthesis see: Tetrahedron Lett. 1997, 38 (23), 4091-4094), (33.1 g, 0.108 mol)] in THF (750 ml) under argon was cooled to – 45°C. To this cooled solution was added via dropping funnel a 1M solution of vinyl magnesium bromide in THF (345 ml, 0.345 mol) over 20 minutes. The mixture was stirred at this temperature for 40 minutes followed by slow addition of sat. NH_4Cl solution and the resulting mixture extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude material was purified by column chromatography on silica gel (acetone/toluene gradient) to afford the title compound (D3) (3.55 g, 11%), δ_H ($CDCl_3$) 1.50 (9H, s), 3.06 (4H, t, J = 5.0 Hz), 3.65 (4H, t, J = 4.8 Hz), 6.56 (1H, m), 6.83 (1H, d, J = 7.5 Hz), 7.07 (1H, t, J = 7.7 Hz), 7.20 (1H, m), 7.39 (1H, d, J = 7.9 Hz), 8.28 (1H, br s).

Description 4: 4-[3-(3-Chlorophenyl)sulfonyl-1H-indol-7-yl]piperazine-1-carboxylic acid tert-butyl ester (D4)

To a suspension of sodium hydride (0.20 g, 5.0 mmol), in DMF (15 ml) under argon was added 4-(1H-indol-7-yl)piperazine-1-carboxylic acid tert-butyl ester (D3) (1.0 g, 3.3 mmol) in portions over 5 minutes. After complete addition, the mixture was stirred at room temperature for a further 10 minutes and a solution of bis-(3-chlorophenyl) disulfide (1.04 g, 3.6 mmol) in DMF (5 ml) was then added over 5 minutes. The solution was stirred for 2 hours followed by careful addition of water (100 ml) and then diethyl ether (100 ml). The organic layer was separated,

washed with water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to provide 4-[3-(3-chlorophenyl)sulfanyl-1-methyl-1H-indol-7-yl]piperazine-1-carboxylic acid tert-butyl ester (1.16 g, 79%). This was dissolved in dichloromethane (40 ml) and to it added 3-chloroperbenzoic acid (2.1 g, 9.1 mmol) portion wise over 5 minutes. The resulting mixture was stirred at ambient temperature for 18 hours and then diluted with dichloromethane (40 ml), washed with saturated aqueous sodium metabisulfite (100 ml), sat. $NaHCO_3$ solution (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with dichloromethane to afford the title compound (D4) (930 mg, 75%) , δ_H ($CDCl_3$) 1.49 (9H, s), 3.00 (4H, t, J = 5.1 Hz), 3.63 (4H, t, J = 4.9 Hz), 6.94 (1H, d, J = 7.0 Hz), 7.22 (1H, t, J = 7.9 Hz), 7.40-7.47 (2H, m), 7.64 (1H, d, J = 8.0 Hz), 7.89-7.93 (2H, m), 7.98 (1H, t, J = 1.5 Hz), 9.13 (1H, br s).

Description 5: 4-[3-(3-Chlorophenyl)sulfonyl-1-methyl-1H-indol-7-yl]piperazine-1-carboxylic acid tert-butyl ester (D5)

A mixture of 4-[3-(3-chlorophenyl)sulfonyl-1H-indol-7-yl]piperazine-1-carboxylic acid tert-butyl ester (D4) (115 mg, 0.24 mmol) and KOH (17 mg, 0.3 mmol) in ethanol (2 ml) was stirred at room temperature for 30 minutes and the solvent removed *in vacuo*. The residue was dissolved in acetone (2 ml) and dimethylsulfate (23 µL, 0.24 mmol) added to the solution. The mixture was stirred at ambient temperature for 1 hour followed by addition of dichloromethane (20 ml). The organic phase was washed with water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material by column chromatography on silica gel (petroleum ether (40-60)/ethylacetate gradient) gave the title compound (D5) (70 mg, 60%), δ_H ($CDCl_3$) 1.49 (9H, s), 2.85-2.91 (2H, m), 3.02-3.09 (4H, m), 4.12 (2H, m), 4.21 (3H, s), 7.05 (1H, d, J = 6.7 Hz), 7.23 (1H, t, J = Hz), 7.36-7.46 (2H, m), 7.69 (2H, m), 7.91 (1H, m), 7.96 (1H, t, J = 1.8 Hz).

Description 6: 1-(5-Chloro-2-nitro)phenyl-4-methylpiperazine (D6)

A solution of 4-chloro-2-fluoronitrobenzene [Fluorochem] (863mg, 5mmol), in dichloromethane (5ml) was treated with triethylamine (505mg, 5mmol) and N-methylpiperazine (5mmol, 500mg) at 0°C. The solution was allowed to warm to room temperature, poured into water (500ml), and extracted with diethyl ether (3 x 100ml). The combined ether extracts were dried ($MgSO_4$), filtered and evaporated and the residue purified by flash chromatography (methanol – dichloromethane) on silica gel to give the title compound (D6) as a yellow solid (440mg, 34%) δ_H ($CDCl_3$) 2.53 (3H, s), 2.57 (4H, t, J = 4.8Hz), 3.10 (4H, t, J = 4.8Hz), 6.96 (1H, dd, J = 2.1Hz, 8.7Hz), 7.07 (1H, d, J = 2.1Hz), 7.76 (1H, d, J = 8.7Hz).

Description 7: 2,3-Dihydro-7-nitro-3-phenylsulfonyl-benzo[b]furan-2-ol (D7)

A solution of 2-hydroxy-3-nitrobenzaldehyde (2.0g, 12mmol) and chloromethylphenyl sulfone (4.6g, 24mmol) in N,N-dimethylformamide (160ml) was added over 5 minutes to a stirred solution of potassium-t-butoxide (45.6g, 400mmol) in N,N-dimethylformamide (200ml) at –40°C. After 2h, the solution was warmed to room temperature and shaken with ethyl acetate (500ml) and 0.5M hydrochloric acid (500ml). The layers were separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to an oil. The oil was purified by chromatography over

silica gel using a solvent gradient of acetone/toluene to afford the title compound (D7) as a gum (2.1g, 55%). Mass Spectrum: m/z $[M-H]^-$ 320 ($C_{14}H_{11}NO_6S$).

Description 8: 7-Nitro-3-phenylsulfonyl-benzo[b]furan (D8)

A solution of 2,3-dihydro-7-nitro-3-phenylsulfonyl-benzo[b]furan-2-ol (D7) (2.1g, 6.5mmol) in conc. sulfuric acid (specific gravity, 1.8) (20ml) and glacial acetic acid (20ml) was heated at 60°C for 10h. After cooling the reaction mixture in an ice bath, it was taken to pH 8 using 10% sodium hydroxide solution, and extracted with chloroform (2 x 150ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D8) as an oil (1.65g, 83%).

δ_H ($CDCl_3$) 7.51-7.67 (4H, m), 8.06 (2H, d, J = 7.4Hz), 8.20 (1H, d, J = 7.9Hz), 8.26 (1H, d, J = 8.1Hz), 8.44 (1H, s).

Description 9: 3-Phenylsulfonyl-benzo[b]furan-7-ylamine (D9)

A solution of 7-nitro-3-phenylsulfonyl-benzo[b]furan (D8) (1.5g, 5.0mmol) in ethanol (110ml) and N,N-dimethylformamide (40ml) was stirred at ambient temperature with 10% palladium on carbon (1.5g) under one atmosphere of hydrogen for 3h. The mixture was filtered to remove the catalyst and the filtrate concentrated *in vacuo* to an oil. The oil was purified by chromatography over silica gel eluting with a solvent gradient of acetone/toluene to afford the title compound (D9) (0.51g, 37%). Mass Spectrum: m/z $[MH]^+$ 274 ($C_{14}H_{11}NO_3S$).

Description 10: 7-Bromo-3-phenylsulfanyl-benzo[b]thiophene (D10)

A solution of 7-bromo-3-hydroxy-benzo[b]thiophene [J. Indian Chem. Soc. **43** (9) 597 1966] (1.15g, 5.0 mmol), thiophenol (0.56g, 5.0 mmol) and p-toluene sulfonic acid (0.1g catalytic), in dry benzene (30 ml) was refluxed with the condensate passing through 3A molecular sieves (10 ml), in a Soxhlet device for 16h. The solvent was removed and the residue was chromatographed on silica using pentane as eluant to afford the title compound (D10) (710 mg, 50% yield). δ_H ($CDCl_3$) 7.23-7.12 (5H, m), 7.25 (1H, t, J = 8.1 Hz), 7.54 (1H, d, J = 7.6 Hz), 7.75 (2H, m).

Description 11: 7-Bromo-3-phenylsulfonyl-benzo[b]thiophene (D11)

7-Bromo-3-phenylsulfanyl-benzo[b]thiophene (D10) (125 mg, 0.39 mmol) and magnesium mono-peroxyphthalate (268 mg, 0.43 mmol) were stirred at room temperature in methanol (5 ml) and dichloromethane (20 ml) for 16h. The solvent was removed and the residue was triturated under dichloromethane then filtered. The solvent was removed to afford crude product which was purified by chromatography on silica using dichloromethane as eluant to afford the title compound (D11) (125 mg, 91% yield). δ_H ($CDCl_3$) 7.36 (1H, t, J = 7.9 Hz), 7.59-7.49 (4H, m), 8.08 (2H, dd, J = 0.3 Hz, 8.4 Hz), 8.18 (1H, d, J = 7.7 Hz), 8.50 (1H, s).

Description 12: 7-(4-tert-Butyloxycarbonyl-1-piperazinyl)- 3-phenylsulfonyl-benzo[b]thiophene (D12)

A catalyst suspension was prepared by sonicating palladium acetate (5mg, 0.022 mmol), cesium carbonate (98 mg, 0.3 mmol), and BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] (20 mg, 0.032 mmol) in dioxane (5 ml) under argon for 45 mins at 35°C. 7-Bromo-3-phenylsulfonyl-

benzo[b]thiophene, (D11) (66 mg, 0.19 mmol), and 1-tert-butyloxycarbonyl-piperazine (56 mg, 0.3 mmol) was added to the above catalyst and the stirred mixture heated to 100°C under argon for 16h. The mixture was filtered and the solvent removed. The crude product was purified by chromatography on silica with a pentane / ethyl acetate mixture (3:1), as eluant to afford the title compound (D12) (48 mg, 53% yield). δ_H ($CDCl_3$) 1.48 (9H, s), 3.08 (4H, m), 3.63 (4H, m), 7.00 (1H, d, J = 7.6 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.51 (3H, m), 7.90 (1H, d, J = 8.0 Hz), 8.03 (2H, d, J = 7.3 Hz), 8.44 (1H, s).

Descriptions 13 and 14: 7-(4-tert-Butyloxycarbonyl-1-piperazinyl)-6-chloro-3-phenylsulfonyl-benzo[b]thiophene (D13) and 7-(4-tert-butyloxycarbonyl-1-piperazinyl)-4-chloro-3-phenylsulfonyl-benzo[b]thiophene (D14)

To a solution of 7-(4-tert-butyloxycarbonyl-1-piperazinyl)- 3-phenylsulfonyl-benzo[b]thiophene (D12) (244 mg, 0.53 mmol) in glacial acetic acid (10 ml) was added N-chlorosuccinimide (71 mg, 0.53 mmol) portionwise over 10 minutes. The reaction mixture was heated at 60° C for 18 h under argon. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (20 ml), water (10 ml) and adjusted to pH 8 with saturated sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica eluting with 15-20% ethyl acetate / hexane to yield the two title compounds, listed in elution order:

(D13) (131 mg, 50%) was afforded as a colourless oil, δ_H ($CDCl_3$) 1.49 (9H, s), 3.00-3.50 (6H, m), 3.90-4.00 (2H, m), 7.40 (1H, d, J=8.6 Hz), 7.49-7.53 (2H, m), 7.55-7.57 (1H, m), 7.92 (1H, d, J=8.6 Hz), 8.00-8.03 (2H, m), 8.40 (1H, s).

(D14) (49 mg, 19%) was afforded as a white solid, δ_H ($CDCl_3$) 1.49 (9H, s), 3.04-3.06 (4H, m), 3.64-3.66 (4H, m), 6.97 (1H, d, J=8.24), 7.34 (1H, d, J=8.20 Hz), 7.48-7.52 (2H, m), 7.56-7.58 (1H, m), 7.87-7.89 (2H, m), 8.73 (1H, s).

Description 15: 7-(4-tert-Butoxycarbonyl-piperazin-1-yl)-1H-indole-1-carboxylic acid tert-butyl ester (D15)

To a stirred solution of 4-(1 H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D3) (1g, 3.3mmol) in dry dichloromethane (30 ml) was added di-tert-butyl dicarbonate (1.08 g, 5 mmol) and N,N-dimethylaminopyridine (203 mg, 1.66 mmol) and the reaction mixture stirred under argon for 18 hours. The reaction mixture was concentrated *in vacuo* and crude material was purified by column chromatography on silica eluting with 20% ethyl acetate / petroleum ether (40-60 °C) to afford the title compound (D15) as a colourless oil. (1.35 g, 100%), δ_H ($CDCl_3$) 1.48 (9H, s), 1.63 (9H, s), 2.98 (4H, m), 3.63 (4H, m), 6.53 (1H, d, J=3.7 Hz), 6.90 (1H, d, J=7.3 Hz), 7.15-7.25 (2H, m), 7.46 (1H, d, J=3.7 Hz). Mass Spectrum: m/z $[MH]^+$ 402 ($C_{22}H_{31}N_3O_4$).

Description 16: 7-(4-tert-Butoxycarbonyl-piperazin-1-yl)-2-methyl-1H-indole-1-carboxylic acid tert-butyl ester (D16)

To a stirred solution of 7-(4-tert-butoxycarbonyl-piperazin-1-yl)-1H-indole-1-carboxylic acid tert-butyl ester (D15) (0.622 g, 1.55 mmol) in tetrahydrofuran (5 ml) at -78°C under argon was added t-butyllithium dropwise (1.09 ml, 1.9 mmol, 1.7M solution in hexanes). Stirring was continued for 1h at the same temperature before the reaction was quenched by addition of iodomethane (0.116 ml, 1.9 mmol). The reaction was then slowly warmed to room temperature and stirred for 18h. The reaction was poured into aqueous ammonium chloride (10 ml) and the whole was extracted with dichloromethane (20ml). The organic phase was washed with saturated brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D16) (0.653 g, 100%). δ_H ($CDCl_3$) 1.49 (9H, s), 1.64 (9H, s), 2.46 (3H, s), 2.95-2.97 (4H, m), 3.58 (4H, m), 6.24 (1H, s), 6.94 (1H, d, J=7.5 Hz), 7.11 (1H, t, J=7.6 Hz), 7.20 (1H, d, J=7.6 Hz). Mass Spectrum: m/z $[MH]^+$ 416 ($C_{23}H_{33}N_3O_4$).

Description 17: 4-(2-Methyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D17)

To a stirred solution of 7-(4-tert-butoxycarbonyl-piperazin-1-yl)-2-methyl-1H-indole-1-carboxylic acid tert-butyl ester (D16) (473 mg, 1.1mmol) in 1,4 dioxane (5 ml) was added 4M aqueous hydrochloric acid (5 ml) and the reaction was stirred under argon for 1.5 hours at 80° C. The reaction mixture was concentrated *in vacuo* to yield a purple solid (285 mg). The solid was dissolved in dichloromethane (10 ml) and to the stirred solution was sequentially added dropwise triethylamine (0.166 ml, 1.2 mmol) and a solution of di-t-butyl dicarbonate (260 mg, 1.2mmol) in dry dichloromethane (5 ml). The reaction mixture was stirred at ambient temperature under argon for 15 minutes before being diluted with dichloromethane (10 ml) and water (10 ml). After vigorously shaking the mixture, the layer were separated and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica eluting with 15% ethyl acetate / petroleum ether (40-60° C) to afford the title compound (D17) (196 mg, 57%), δ_H ($CDCl_3$) 1.50 (9H, s), 2.46 (3H, s), 3.02-3.06 (4H, m), 3.63-3.67 (4H, m), 6.21 (1H, s), 6.75 (1H, d, J= 7.6 Hz), 7.00 (1H, t, J=7.7 Hz), 7.26 (1H, d, J=7.2 Hz), 8.00 (1H, br s). Mass Spectrum: m/z $[MH]^+$ 316 ($C_{18}H_{25}N_3O_2$).

Description 18: 4-(2-Methyl-3-phenylsulfanyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D18)

To a stirred suspension of sodium hydride (38mg, 0.94mmol) in dry N,N-dimethylformamide (5 ml) was added a solution of 4-(2-methyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D17) (198mg, 0.63mmol) in dry N,N-dimethylformamide (5 ml) dropwise over 5 minutes. After stirring at room temperature for 10 minutes under argon, a solution of phenyl disulfide (151 mg, 0.7mmol) in dry N,N-dimethylformamide (2 ml) was added dropwise and the reaction mixture was stirred at room temperature for a further 4 hours. The reaction mixture was diluted with ether (20 ml) and water (20 ml) and the whole was shaken and separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica eluting with 20% ethyl acetate / petroleum ether (40-60 °C) to afford the title compound (D18) as an oil. (119 mg, 45%) δ_H ($CDCl_3$) 1.50 (9H, s), 2.54 (3H, s), 3.05-3.09 (4H, m), 3.65-3.69 (4H, m), 6.85 (1H, d, J=7.6 Hz), 7.00-7.06 (4H, m), 7.10-7.17 (2H, m), 7.30 (1H, d, J=7.8 Hz), 8.38 (1H, br s). Mass Spectrum: m/z $[MH]^+$ 424 ($C_{24}H_{29}N_3O_2S$).

Description 19: 4-(2-Methyl-3-phenylsulfonyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D19)

To a solution of 4-(2-methyl-3-phenylsulfanyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D18) (119 mg, 0.28 mmol) in dry dichloromethane (5 ml) was added 3-chloroperoxybenzoic acid (291 mg, 0.84 mmol) in a single portion. The reaction mixture was stirred under argon at room temperature for 2 hours before being diluted with dichloromethane (10 ml), water (10 ml) and sodium disulfite (20ml of 10% w/v solution). The whole was shaken and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica eluting with 40-50% ethyl acetate / petroleum ether (40-60 °C) gradient to afford the title compound (D19) (94mg, 74%). δ_H ($CDCl_3$) 1.48 (9H, s), 2.76 (3H, s), 2.98-3.02 (4H, m), 3.61-3.65 (4H, m), 6.88 (1H, d, J=7.7Hz), 7.17 (1H, t, J=7.9Hz), 7.40-7.49 (3H, m), 7.79 (1H, d, J=8.0Hz), 7.95-7.98 (2H, m), 9.18 (1H, br s). Mass Spectrum: m/z $[M-H]^-$ 454 ($C_{24}H_{29}N_3O_4S$).

Description 20: 4-(1,2-Dimethyl-3-phenylsulfonyl-1H-indole-7-yl)piperazine-1-carboxylic acid tert-butyl ester (D20)

To a solution of 4-(2-methyl-3-phenylsulfonyl-1H-indol-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (D19) (92 mg, 0.2 mmol) in ethanol (2 ml) under argon was added powdered potassium hydroxide (17 mg, 0.3 mmol). After 5 minutes of stirring at room temperature the reaction mixture was concentrated *in vacuo*. The residual oil was re-suspended in dry acetone (2 ml) and dimethylsulphate (29 µl, 0.3 mmol) was added dropwise. The reaction mixture was stirred at room temperature under argon for 18h and then diluted with dichloromethane (2x10 ml), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography on silica eluting with 20-30% ethyl acetate / petroleum ether (40-60 °C) gradient to afford the title compound (D20) (72 mg, 77%), δ_H ($CDCl_3$) 1.49 (9H, s), 2.74 (3H, s), 2.82-2.86 (2H, m), 3.02-3.05 (4H, m), 4.11-4.13 (2H, m), 4.15 (3H, s), 6.98 (1H, d, J=7.4 Hz), 7.15 (1H, t, J= 7.9 Hz), 7.41-7.48 (3H, m), 7.92-7.97 (3H, m). Mass Spectrum: m/z $[MH]^+$ 470 ($C_{25}H_{31}N_3O_4S$).

Description 21: 5-Chloro-7-(4-methylpiperazin-1-yl)-1H-indole (D21)

1-(5-Chloro-2-nitro)phenyl-4-methylpiperazine (D6) (644mg, 2.5 mmol), was dissolved in THF (20ml) and cooled to –45°C. A solution of vinylmagnesium bromide (1M in THF, 8.25ml) was introduced in one portion at such a rate as to maintain the temperature between –40 °C and –45°C. The mixture was maintained within this temperature range for 30 minutes then poured into saturated aqueous ammonium chloride solution (100ml). The mixture was extracted with dichloromethane (3 x 50ml) and the combined extracts dried ($MgSO_4$), filtered and evaporated to a brown oil. The residue was co-evaporated with toluene (20ml) and the resulting oil subjected to purification by chromatography on silica gel (eluting with aqueous ammonia – methanol – dichloromethane) to obtain the title compound (D21) as a brown gum (100mg, 13%).
δ_H ($CDCl_3$) 2.39 (3H, s), 2.64 (4H, t, J = 4.6Hz), 3.13 (4H, t, J = 4.6Hz), 6.48 (1H, t, J = 2.7Hz), 6.78 (1H, d, J = 1.5Hz), 7.18 (1H, t, J = 2.7 Hz), 7.33 (1H, d, J = 1.5Hz), 8.3 (1H, br s).

Description 22: 5-Chloro-3-(3-chlorophenyl)sulfanyl-7-(4-methyl-piperazin-1-yl)-1H-indole (D22)

A suspension of sodium hydride (40% oil dispersion, 20mg, 0.5 mmol) in DMF (1ml) was treated with solution of 5-chloro-7-(4-methylpiperazin-1-yl)-1H-indole (D21) (87mg, 0.24 mmol) in DMF (1ml). After effervescence ceased, bis-(3-chlorophenyl)-disulphide (110mg, 0.39mmol) was introduced and the mixture stirred for 17 hours. The solution was evaporated and the residue purified by flash chromatography on silica gel (eluting with methanol – dichloromethane – aqueous ammonia) to form the title compound (D22) as a colourless solid (95mg, 68%). δ_H ($CDCl_3$) 2.40 (3H, s), 2.66 (4H, t, J = 4.7Hz), 3.15 (4H, t, J = 4.7Hz), 6.85 (1H, d, J = 1.7Hz), 6.93 (1H, dd), 7.01-7.10 (3H, m), 7.27 (1H, d, J = 1.6 Hz), 7.46 (1H, d, J = 2.6Hz), 8.6 (1H, br s).

Example 1: 3-(1H-Indole-1-sulfonyl)-7-(4-methyl-piperazin-1-yl)-1H-indole (E1)

3-(1H-Indole-1-sulfonyl)-1H-7-indol-7-ylamine (D2) (0.5 g, 1.6 mmol) was dissolved in n-butanol (20 ml) followed by addition of sodium carbonate (0.85 g, 8.0 mmol) and methchlorethamine hydrochloride (0.47 g, 2.4 mmol). The resulting suspension was heated to reflux for 48 hours. After allowing to cool, the solvent was removed *in vacuo*, the residue taken up in dichloromethane (100 ml) and washed with saturated sodium hydrogencarbonate solution (2x50 ml). The organic phase was dried ($MgSO_4$), filtered and the solvent evaporated. The crude was purified by column chromatography on silica, eluting with a methanol/dichloromethane gradient to afford the title compound (E1) (0.25 g, 40%), MS: m/z $(M-H)^-$ 393, $C_{21}H_{22}N_4O_2S$ requires 394.

Example 2: 3-(1H-Indole-1-sulfonyl)-7-piperazin-1-yl-1H-indole (E2)

To a solution of 3-(1H-Indole-1-sulfonyl)-7-(4-methyl-piperazin-1-yl)-1H-indole (E1) (0.1 g, 0.25 mmol) in dry 1,2-dichloroethane (5 ml) was added N,N-diisopropylethylamine (0.11 ml, 0.76 mmol) and 1-chloroethyl chloroformate (83 µl, 0.76 mmol). The solution was stirred at 80°C for 30 minutes, cooled to ambient temperature and then concentrated *in vacuo*. The residue was dissolved in methanol (10 ml) and the solution heated to reflux for 1 hour. After concentrating the mixture *in vacuo*, the residue was dissolved in dichloromethane (20 ml) and washed with saturated sodium hydrogencarbonate solution (20 ml) and water (2 x 10 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel, eluting with a methanol/dichloromethane gradient to afford the title compound (E2) (55 mg, 57%), δH (CD_3OD) 3.22 (4H, br s), 3.42 (4H, br s), 6.62 (1H, d, J = 3.7 Hz), 6.92 (1H, d, J = 7.7 Hz), 7.12-7.17 (2H, m), 7.25 (1H, t, J = 8.2 Hz), 7.49 (1H, d, J = 7.8 Hz), 7.59 (1H, d, J = 8.1 Hz), 7.76 (1H, d, J = 3.7 Hz), 7.96 (1H, d, J = 8.3 Hz), 8.09 (1H, s). MS: m/z $(M-H)^-$ 379, $C_{20}H_{20}N_4O_2S$ requires 380.

Example 3: 3-(3-Chlorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole hydrochloride (E3)

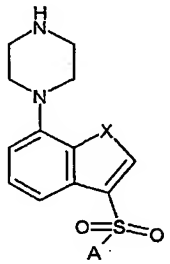
To a solution of 4-[3-(3-chlorophenyl)sulfonyl-1-methyl-1H-indol-7-yl]piperazine-1-carboxylic acid tert-butyl ester (D5) (52 mg, 0.11 mmol) in 1,4-dioxane (6 ml) was added 3M HCl (6 ml) and the resulting solution heated to 60 °C for 60 minutes. After allowing to cool to ambient temperature, the mixture was concentrated *in vacuo* to afford the title compound (E3) (39 mg,

90%), δ_H (CD_3OD) 3.19 (2H, m), 3.33-3.35 (2H, m), 3.36-3.50 (4H, m), 4.24 (3H, s), 7.20-7.27 (2H, m), 7.52 (1H, t, J = 7.9 Hz), 7.59 (1H, m), 7.71 (1H, d, J = 7.8 Hz), 7.92-7.97 (2H, m), 8.00 (1H, s). Mass Spectrum: m/z $[MH]^+$ 390 ($C_{19}H_{20}ClN_3O_2S$).

Examples 4-17 (E4-E17)

3-(Phenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E4);
3-(2-Fluorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E5);
3-(2-Chlorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E6);
3-(2-Cyanophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E7);
3-(3-Fluorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E8);
3-(2-Trifluoromethylphenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole (E9);
3-(Phenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E10);
3-(3-Chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E11);
3-(2-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E12);
3-(4-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E13);
3-(3-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E14);
3-(2-Pyridyl)sulfonyl-7-piperazin-1-yl-1H-indole (E15);
3-(2-Chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E16);
3-(2-Cyanophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E17);

Examples 4-9 were prepared using analogous procedures to those described in D4 followed by D5 and then deprotection in an analogous manner to that described in Example 3 (E3).
Examples 10-17 were prepared using an analogous procedure to that described in D4 followed by deprotection in an analogous manner to that described in Example 3.



Example	X	A	m/z $[MH]^+$	Formula
E4	NMe	phenyl	356	$C_{19}H_{21}N_3SO_2$
E5	NMe	2-fluorophenyl	374	$C_{19}H_{20}FN_3SO_2$
E6	NMe	2-chlorophenyl	390/392	$C_{19}H_{20}ClN_3SO_2$
E7	NMe	2-cyanophenyl	381	$C_{20}H_{20}N_4SO_2$
E8	NMe	3-fluorophenyl	374	$C_{19}H_{20}FN_3SO_2$
E9	NMe	2-trifluoromethylphenyl	424	$C_{20}H_{20}F_3N_3SO_2$
E10	NH	phenyl	340(M-H)	$C_{18}H_{19}N_3SO_2$
E11	NH	3-chlorophenyl	376/378	$C_{18}H_{18}ClN_3SO_2$
E12	NH	2-fluorophenyl	360	$C_{18}H_{18}FN_3SO_2$
E13	NH	4-fluorophenyl	360	$C_{18}H_{18}FN_3SO_2$
E14	NH	3-fluorophenyl	360	$C_{18}H_{18}FN_3SO_2$

E15	NH	2-pyridyl	343	$C_{17}H_{18}N_4SO_2$
E16	NH	2-chlorophenyl	376/378	$C_{18}H_{18}ClN_3SO_2$
E17	NH	2-cyanophenyl	367	$C_{19}H_{18}N_4SO_2$

Example 18: 1,2-Dimethyl-3-phenylsulfonyl-7-piperazin-1-yl-1H-indole, hydrochloride (E18)

4-(1,2-Dimethyl-3-phenylsulfonyl-1H-indole-7-yl)piperazine-1-carboxylic acid tert-butyl ester (D20) (64 mg, 0.14 mmol) was dissolved in 1,4-dioxane (1 ml). 4M aqueous hydrochloric acid (1 ml) was added and the reaction mixture stirred at 80°C under argon for 1.5h. The solvent was evaporated *in vacuo* to afford the title compound (E18) as a white solid (45 mg, 79%), δ_H ($[CD_3]_2SO$) 2.72 (3H, s), 3.02-3.39 (8H, m), 4.09 (3H, s), 7.01 (1H, d, J=7.3Hz), 7.16 (1H, t, J=7.9 Hz), 7.51-7.63 (3H, m), 7.75 (1H, d, J=7.9 Hz), 7.89-7.97 (2H, m), 9.23 (1H, br s), 9.43 (1H, br s). Mass Spectrum: m/z $[MH]^+$ 370 ($C_{20}H_{23}N_3O_2S$).

Example 19: 4-Methyl-1-(3-phenylsulfonyl-benzo[b]furan-7-yl)piperazine trifluoroacetate (E19)

A mixture of 3-phenylsulfonyl-benzo[b]furan-7-ylamine (D9)(0.273, 1.0mmol), methchlorethamine hydrochloride (0.243g, 1.3mmol) and anhydrous sodium carbonate (0.53g, 5.0mmol) in n-butanol (7ml) were stirred at reflux under argon for 36h. The mixture was diluted with dichloromethane (25ml) and washed with water (25ml). The organic phase was dried ($MgSO_4$), concentrated to an oil and purified by HPLC chromatography on a 25cm x 21mm column packed with 12 micron SUPELCOSIL ABZ + eluting with acetonitrile/water/0.1% trifluoroacetic acid solvent gradient to afford the title compound (E19) as a solid (60mg, 0.17mmol, 17%).

δ_H (CD_3OD) 2.98 (3H, s), 3.18 (2H, br t, J = 12Hz), 3.36 (2H, br t, J = 12Hz), 3.63 (2H, br d, J = 12Hz), 3.95 (2H, br d, J = 12Hz), 6.97 (1H, d, J = 7.8Hz), 7.30 (1H, t, J = 7.9Hz), 7.45 (1H, d, J = 8.5Hz), 7.57-7.67 (3H, m), 8.07 (2H, d, J = 7.2Hz), 8.54 (1H, s).

Example 20: 1-(3-Phenylsulfonyl-benzo[b]furan-7-yl)piperazine, hydrochloride (E20)

To a solution of 4-methyl-1-(3-phenylsulfonyl-benzo[b]furan-7-yl)piperazine trifluoroacetate (E19) (0.132g, 0.37mmol) in 1,2-dichloroethane (1.5ml) was slowly added 1-chloroethyl chloroformate (0.06ml, 0.6mmol) followed by N,N-di-isopropylethylamine (0.1ml, 0.6mmol) under argon at ambient temperature. The solution was heated at reflux for 24h and then further quantities of 1-chloroethyl chloroformate (0.16ml, 1.5mmol) and N,N-di-isopropylethylamine (0.26ml, 1.5mmol) were added and reflux was maintained for a further 24h. The reaction mixture was concentrated *in vacuo* to an oil, which was purified by chromatography over silica gel eluting with a solvent gradient of ethyl acetate/hexane. Column fractions containing the major component (Thin layer chromatography on silica gel plates: Rf 0.58; ethyl acetate/hexane 4:1) were pooled and concentrated *in vacuo* to an oil. A solution of this oil in methanol(1.5ml) was heated at reflux for 1h under argon and then concentrated *in vacuo* to afford a white solid. The solid was recrystallised from dichloromethane and 1M hydrogen chloride in diethyl ether to give the title compound (E20) (41mg, 0.11mmol, 29%).

δ_H (CD_3OD) 3.42-3.44 (4H, m), 3.52-3.54 (4H, m), 7.00 (1H, d, J = 7.8Hz), 7.30 (1H, t, J = 2.7Hz), 7.44 (1H, d, J = 7.4Hz), 7.58-7.68 (3H, m), 8.08 (2H, 7.3Hz), 8.57 (1H, s). Mass Spectrum: m/z $[MH]^+$ 343 ($C_{18}H_{18}N_2O_3S$).

Example 21: 3-Phenylsulfonyl-7-(1-piperazinyl)benzo[b]thiophene hydrochloride (E21)
7-(4-tert-Butyloxycarbonyl-1-piperazinyl)-3-phenylsulfonyl-benzo[b]thiophene (D12) (45 mg, 0.1 mmol) was dissolved in dioxane (1 ml), and treated with 4M hydrochloric acid (1 ml) with stirring at 80°C for 5 mins. The solvents were removed and purification was effected by ion exchange chromatography (Varian Mega Bond Elut SCX) using methanol then 15% ammonium hydroxide in methanol. After removal of solvents the product was treated with methanol / ethereal hydrogen chloride and the solvents removed to afford the title compound (E21) (19 mg, 49% yield). δ_H (CD_3OD) 8.67 (1H, s) 8.03 (2H, dd, J = 8.6 Hz, 1.5 Hz), 7.93 (1H, d, J = 8.1 Hz) 7.64-7.47 (4H, m), 7.21 (1H, d, J = 7.2 Hz), 3.42 (4H, m) 3.36 (4H, m). Mass Spectrum: m/z $[MH]^+$ 359 ($C_{18}H_{18}N_2O_2S_2$).

Example 22: 6-Chloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride (E22)
7-(4-tert-Butyloxycarbonyl-1-piperazinyl)-6-chloro-3-phenylsulfonyl-benzo[b]thiophene (D13) (131 mg, 0.27mmol) was dissolved in 1,4-dioxane (2 ml) and aqueous 4M HCl (2 ml) was added. The reaction mixture was stirred under argon at 80° C for 1.5h and solvent evaporated *in vacuo* to afford the title compound (E22) as a white solid (107 mg, 93%), δ_H (CD_3OD) 3.32-3.51 (6H, m), 3.84 (2H, m), 7.53-7.67 (4H, m), 8.04-8.07 (3H, m), 8.71 (1H, s). Mass Spectrum: m/z $[MH]^+$ 393, 395 ($C_{18}H_{17}ClN_2O_2S_2$).

Example 23: 4-Chloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride (E23)
The title compound (E23) was prepared in quantitative yield (37 mg) from 7-(4-tert-butyloxycarbonyl-1-piperazinyl)-4-chloro 3-phenylsulfonyl-benzo[b]thiophene (D14) (42 mg, 0.086 mmol) as described in Example 1. δ_H ($[CD_3]_2SO$) 3.29-3.34 (8H, m), 7.25 (1H, d, J=8.2 Hz), 7.48 (1H, d, J=8.2 Hz), 7.60-7.66 (2H, m), 7.69-7.73 (1H, m), 7.83-7.85 (2H, m), 9.06 (3H, s). Mass Spectrum: m/z $[MH]^+$ 393, 395 ($C_{18}H_{17}ClN_2O_2S_2$).

Example 24: 4,6-Dichloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride (E24)
To a solution of 7-(4-tert-butyloxycarbonyl-1-piperazinyl)- 3-phenylsulfonyl-benzo[b]thiophene (D12) (285 mg, 0.62 mmol) in glacial acetic acid (10 ml) was added N-chlorosuccinimide (166 mg, 1.24 mmol) portionwise over 10 minutes. Reaction mixture was heated at 60° C for 18 h under argon. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (20 ml), water (10 ml) and adjusted to pH 8 with saturated sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford an oil, which was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane / methanol followed by HPLC chromatography on a 25cm x 21mm column packed with 12 micron SUPELCOSIL ABZ+,

eluting with an acetonitrile / water/ 0.1% trifluoroacetic acid solvent gradient. The resulting solid was dissolved in MeOH (5 ml) and treated with 1M hydrogen chloride in diethyl ether (0.2 ml, 4 equiv.) to afford the title compound (E24) as a white solid (22 mg, 8%)
δ_H (CD_3OD) 3.35-3.62 (6H, m), 3.91-4.00 (2H, m), 7.62 (1H, s), 7.64-7.80 (3H, m), 7.95-7.99 (2H, m), 8.96 (1H, s). Mass Spectrum: m/z $[MH]^+$ 427 429, 431 ($C_{18}H_{16}Cl_2N_2O_2S_2$).

Example 25: 5-Chloro-3-(3-chlorophenyl)sulfonyl-7-(4-methyl-piperazin-1-yl)-1H-indole (E25)

A solution of 5-chloro-3-(3-chlorophenyl)sulfanyl-7-(4-methyl-piperazin-1-yl)-1H-indole (D22) (90mg, 0.21mmol) in trifluoroacetic acid (1.5 ml) was treated with hydrogen peroxide (27% aqueous, 100mg), and the mixture stirred at ambient for 2 hours. The mixture was poured into saturated sodium sulphite (5ml), treated with saturated aqueous sodium carbonate (5ml) and extracted into dichloromethane (3 x 10ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated and the residue purified by flash chromatography on silica gel (eluting with dichloromethane – methanol – aqueous ammonia) to give the title compound (E25) (39 mg, 40%) as a colourless solid.
δ_H ($CDCl_3$) 2.38 (3H, s), 2.64 (4H, t, 4.8Hz), 3.09 (4H, t, 4.8Hz), 6.9 (1H, d, J = 1.7Hz), 7.43 (1H, t, J = 7.8Hz), 7.50 (1H, dd, J = 1.2, 3Hz), 7.60 (1H, d, J = 1.7Hz), 7.88-7.95 (3H, m), 8.9 (1H, br s); m/z $[MH]^+$ 424, 426, 428, ($C_{19}H_{19}Cl_2N_3O_2S$).

Example 26: 5-Chloro-3-(3-chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole (E26)

A solution of 5-chloro-3-(3-chlorophenyl)sulfonyl-7-(4-methyl-piperazin-1-yl)-1H-indole (E25) (40mg, 0.09 mmol) in dichloromethane (0.5ml) was treated with 1-chloroethyl chloroformate (50µl) and Hunig's base (100µl). After 2 hours, methanol (5ml) and potassium carbonate (70mg, 0.5mmol) were added and the mixture heated to reflux for 2 hours. The cooled mixture was evaporated, treated with acetic acid (0.5ml), evaporated, and the residue subjected to flash chromatography on silica gel (eluting with dichloromethane – methanol aqueous ammonia) to afford the title compound as a colourless solid (E26) (30mg, 78%)
δ_H ($CDCl_3$ + trace Hunig's base) 3.04 (4H, br s), 3.0 (2H, br s), 3.18 (4H, br s), 6.79 (1H, d, J = 1.6Hz), 7.33-7.42 (2H, m), 7.53 (1H, d, J = 1.6Hz), 7.81-7.87 (3H, m); Mass Spectrum: m/z $[MH]^+$ 410, 412, 414, ($C_{18}H_{17}Cl_2N_3O_2S$).

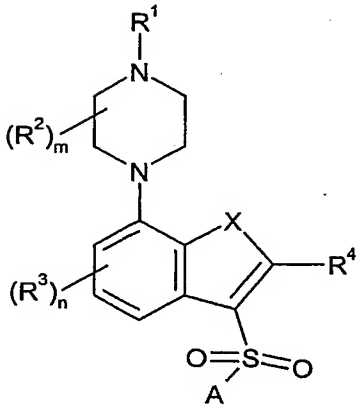
Pharmacological data

Compounds can be tested following the procedures outlined in WO98/27081.
The compounds of Examples E1-E26 were tested and all showed good affinity for the 5-HT_6 receptor, having pKi values > 8.0 at human cloned 5-HT_6 receptors.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;
R^3 independently represents hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;
R^4 represents hydrogen or C_{1-6} alkyl;
R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
m represents an integer from 1 to 4, such that wherein m is an integer greater than 1, said R^2 groups may optionally be linked to form a group CH_2, $(CH_2)_2$ or $(CH_2)_3$;
n represents an integer from 1 to 3;
X represents NH, N-C_{1-6} alkyl, O or S;
A represents a group $-Ar^1$ or $-Ar^2Ar^3$;
Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
or solvates thereof.

2. A compound according to claim 1 wherein R^1 is hydrogen.

3. A compound according to claim 1 or claim 2 wherein R^2 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^3 is hydrogen.

5. A compound according to any one of claims 1 to 4 wherein R^4 is hydrogen.

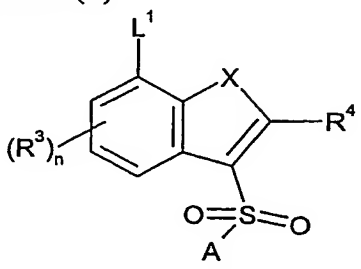
6. A compound according to any one of claims 1 to 5 wherein X is N-CH_3.

7. A compound according to any one of claims 1 to 6 wherein A represents phenyl optionally substituted with one halogen.

8. A compound according to claim 1 which is
3-(1H-Indole-1-sulfonyl)-7-(4-methyl-piperazin-1-yl)-1H-indole;
3-(1H-Indole-1-sulfonyl)-7-piperazin-1-yl-1H-indole;
3-(3-Chlorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole hydrochloride;
3-(Phenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(2-Fluorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(2-Chlorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(2-Cyanophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(3-Fluorophenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(2-Trifluoromethylphenyl)sulfonyl-1-methyl-7-piperazin-1-yl-1H-indole;
3-(Phenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(3-Chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(2-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(4-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(3-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(2-Pyridyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(2-Chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
3-(2-Cyanophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
1,2-Dimethyl-3-phenylsulfonyl-7-piperazin-1-yl-1H-indole, hydrochloride;
4-Methyl-1-(3-phenylsulfonyl-benzo[b]furan-7-yl)piperazine trifluoroacetate;
1-(3-Phenylsulfonyl-benzo[b]furan-7-yl)piperazine, hydrochloride;
3-Phenylsulfonyl-7-(1-piperazinyl)benzo[b]thiophene hydrochloride;
6-Chloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride;
4-Chloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride;
4,6-Dichloro-3-phenylsulfonyl-7-(1-piperazinyl)-benzo[b]thiophene hydrochloride;
5-Chloro-3-(3-chlorophenyl)sulfonyl-7-(4-methyl-piperazin-1-yl)-1H-indole;
5-Chloro-3-(3-chlorophenyl)sulfonyl-7-piperazin-1-yl-1H-indole;
or a pharmaceutically acceptable salt thereof.

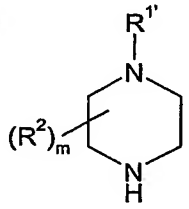
9. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

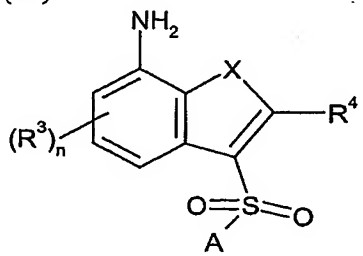
with a compound of formula (III)



(III)

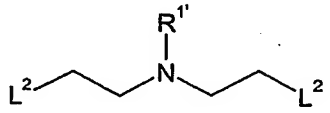
wherein $R^{1'}$ is as defined in claim 1 for R^1 or an N-protecting group, R^2, R^3, R^4, A, X, m and n are as defined in claim 1 and L^1 represents a suitable leaving group; or

(b) forming a compound of formula (I) wherein R^2 represents hydrogen which comprises reacting a compound of formula (IV)



(IV)

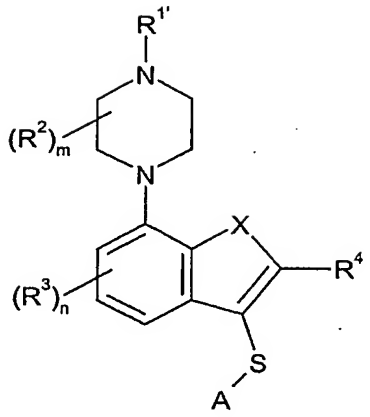
with a compound of formula (V)



(V)

wherein $R^{1'}$ is as defined in claim 1 for R^1 or an N-protecting group, R^3, R^4, X, A and n are as defined in claim 1 and L^2 represents a suitable leaving group; or

(c) oxidation of a compound of formula (VI)



(VI)

wherein $R^{1'}$ is as defined in claim 1 for R^1 or an N-protecting group and R^2, R^3, R^4, A, m, n and X are as defined in claim 1; or

(d) deprotecting a compound of formula (I) which is protected;
and optionally thereafter interconversion to other compounds of formula (I).

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.

11. A compound according to any one of claims 1 to 8 for use in therapy.

12. A compound according to any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

13. The use of a compound of formula (I) as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

14. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

15. A method of treating depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a compound of formula (I) as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08719

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/404 A61K31/343 A61K31/381 A61P25/00 C07D209/40
C07D401/12 C07D307/82 C07D333/66 -

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 941 994 A (HOFFMANN LA ROCHE) 15 September 1999 (1999-09-15) claim 1 ---	1-15
A	WO 98 27081 A (BROMIDGE STEVEN MARK ;KING FRANCIS DAVID (GB); SMITHKLINE BEECHAM) 25 June 1998 (1998-06-25) cited in the application claim 1 ---	1-15
P,A	WO 02 32863 A (BIOVITRUM AB ;JOHANSSON GARY (SE); CALDIROLA PATRIZIA (SE); NILSSO) 25 April 2002 (2002-04-25) claim 1 -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2002	15/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08719

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08719

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		WO	0232863 A1	25-04-2002